through a peptide to which the at least one sugar chain can be added.

21. (New) The heparin-binding protein of claim 20, wherein the heparin-binding protein is a factor belonging to the FGF family.

22. (New) The heparin binding protein of claim 1, wherein the sugar chain is bonded to the heparin-binding protein at a site forming a turn in the secondary structure, or at a site near one of the ends, or at a site at which addition of the sugar chain will not change the tertiary structure of said protein to an extent that the activity of the heparin-binding protein is significantly decreased.

REMARKS

This submission is in response to the Office Action dated October 3, 2000. Consideration of this application, as amended, is respectfully requested.

Attached hereto is a marked up version of the changes made to the claims by the current amendment. The attached page is entitled "Version with markings to show changes made."

An early and favorable action on the merits is earnestly solicited.

STATUS OF THE CLAIMS:

Claims 1-6 and 14 are pending in this application. In applicant's response, dated November 29, 1999, claims 1-6 and 14 were elected and claims 7-13 and 15 were withdrawn from prosecution, as directed to a non-elected invention. Applicants reserve the right to re-introduce claims 7-13 and 15 in a divisional application.

Applicants thank the Examiner for his indication of allowable subject matter in claim 4.

In this response, claim 2 has been canceled without prejudice. Claims 1, 3-6 and 14 have been amended. New claims 16-22 have been added. Therefore, claims 1, 3-22 are now pending

and under examination. No new matter has been added by way of this amendment.

OBJECTIONS:

The Examiner objected to the drawings because the figures allegedly contain Japanese characters. The Examiner also indicated that certain figures have more than one subfigure, and that each must be separately designated.

In response, Applicants respectfully point out that the English translation of the specification, that was submitted in the Response to Missing Parts of the Application on November 16, 1998, provides drawings that contain English characters only. Corrected Figures 5 and 6, which designate separate subfigures 5A and 5B as well as 6A and 6B and also contain English characters only, are provided in this response. In addition, the specification has been amended to make reference to corrected drawings which properly refer to particular sub-parts.

Claim 14 was objected to as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. In response,claim 3, which is one of the claims from which claim 14 is dependent, has been amended to remove its multiple dependency, and Applicants respectfully submit that claim 14, which remains multiple dependent and depends from claims 1 and 3-6, which are all now single-dependent, is now in proper form.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 3, 6 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner alleged that the term "its allied factor" in claim 3 is unclear, and that the disclosure does not indicate what degree of homology would indicate that such factors are "allied."

In response, Applicants have deleted this term from claim 3. Applicants respectfully request that this rejection be withdrawn.

The Examiner alleged that the term "greatly" in claim 6 [1] "is a relative term which renders the claim indefinite." The Examiner stated that

> The term "greatly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure gives no guidance as to how much change in tertiary structure would be considered "great."

Applicants respectfully traverse this rejection. Applicants assert that the term "greatly" is well understood in the art and would imply that the change in the tertiary structure of the protein is such that the activity of the heparin-binding protein is lost or markedly decreased. In fact, Applicants believe that the Examiner himself understood this term, since the Examiner, in discussing the anticipation rejection of claim 6 over Senoo, stated that "inherently, the tertiary structure of the protein cannot be greatly changed if activity is retained in the muteins." (Emphasis added). Thus, Applicants believe that the Examiner understood the meaning of the term "will not change the tertiary structure of the protein greatly" to mean that the tertiary structure of the protein has not been changed to such an extent that activity is no longer retained in the muteins. As such, one with skill in the art would have a similar understanding of this term. Accordingly, Applicants assert that the metes and bounds of claim 6 are clear to anyone with ordinary skill in the art, and Applicants respectfully request that this rejection be withdrawn. In addition, Applicants have added new claim 22 to specifically claim the meaning of the word "greatly," as discussed here.

With respect to the rejection of claim 14 under 35 U.S.C. § 112, second paragraph, as being indefinite, Applicants believe that this rejection should be withdrawn, as either the base claims on which this claim is dependent have been amended to overcome these rejections or the rejections based on those base claims have been obviated. Thus, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 3, 6 and 14 under 35 U.S.C. § 112, second paragraph.

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[1] Applicants respectfully point out that only fifteen (15) claims were filed in this application, and Applicants believe that the Examiner's comments mistakenly referred to claim 16 instead of to claim 6.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 5 was rejected under 35 U.S.C. §112, first paragraph. The Examiner conceded that the specification is enabling for proteins having the SEQ ID NOS recited in part (a), but alleged that the specification does not provide enablement for the deletions, substitutions, additions or modifications of these SEQ ID NOS as recited in part (b). The Examiner further alleged that the specification does not provide adequate direction as to what amino acid residue of these polypeptides is critical for the FGF activity, and that undue experimentation would be required in order to ascertain which amino acids can be deleted, substituted, added or modified without destroying FGF activity.

Applicants respectfully traverse these rejections. Applicants submit that, contrary to the Examiner's assertion, the instant specification does provide enablement for the deletions, substitutions, additions or modifications of these SEQ ID NOS as recited in part (b). The specification sets forth that deletions can be made to the sequence of SEQ ID NO: 27 (210 amino acids), for example, those deletions resulting in SEQ ID NOS: 3 (175 amino acids) or 25 (172 amino acids). These deletions demonstrate that it is possible at least to delete 35 or 38 amino acids from the sequence of SEQ ID NO:27 and retain heparin binding activity and FGF activity.

The specification also shows that additions may be made to the sequences, as shown by the additions to SEQ ID NO:17 (200 amino acids) to produce SEQ ID NOS: 1 (221 amino acids), 21 (254 amino acids) and 23 (281 amino acids). Moreover, single amino acid substitutions are demonstrated by the difference in the sequences shown for SEQ ID NO: 17 and SEQ ID NO: 19 (e.g., the substitution of amino acid residue Pro 43 in SEQ ID NO: 17 for Ser 43 in SEQ ID NO:19). Furthermore, amino acid addition and substitution is also demonstrated in the specification by the sequences shown in SEQ ID NOS: 5 and 29, for example, in the substitution of Asn 127 in SEQ ID NO:29 for Ala 127 and in the addition of Asn 133 in SEQ ID NO: 5, which is inserted before His 133 of SEQ ID NO:29. These additions demonstrate that it is possible to add as few as 1 amino acid or as many as 21, 54 or 81 amino acids to the sequence of SEQ ID NO:17 and still retain heparin binding activity and FGF activity. These substitutions also demonstrate a single amino acid substitution with the resulting sequence retaining heparin

binding activity and FGF activity.

Therefore, because the specification provides sufficient support for the language "deletion, substitution, addition or modification" in claim 5, part (b), as demonstrated above, Applicants respectfully request that this rejection be withdrawn.

Furthermore, with respect to additional deletions, substitutions, additions or modifications, Applicants respectfully submit that the specification does enable any person skilled in the art to make the invention commensurate in scope with these claims. One skilled in the art would readily be able to practice the full scope of the invention as claimed because only routine experimentation is required. As discussed above, Applicants have provided guidance as to the particular regions that may be modified by making substitutions, deletions, and additions, and to the sizes of substitutions, deletions or additions which may be made without loss of activity (see the Sequence Listing). Furthermore, the level of skill in the art, for example knowledge of protein homology and conservative modification of protein sequences, provides guidance to one skilled in the art of possible additional deletions, substitutions, additions or modifications to test. In addition, the specification provides guidance (see, for example, at pages 17-22) as to efficient cloning vectors and expression systems that may be used. Thus, the level of skill in the art is such that any species of the claimed invention can be readily envisioned and prepared.

In addition, the specification provides procedures for assessing the activity of the products having these additional deletions, substitutions, additions or modifications in accordance with the claims and demonstrates that the activity of the claimed heparin-binding proteins may be readily determined. For example, the specification (Test Example 2, pages 23-24) describes an assay for DNA synthesis activity using human umbilical cord-derived vascular endothelial cells, and teaches that the assay can be used as a measure of activity of growth factors such as FGF activity. Figures 5 and 8 demonstrate that the claimed heparin-binding proteins promote DNA synthesis activity.

Thus, the specification provides a description of the necessary procedures so that one skilled in the art could prepare the claimed heparin-binding proteins, i.e., those having deletions, substitutions, additions or modifications, and evaluate them by routine experimentation. Therefore, no undue experimentation would be required to prepare and test any of the heparin-binding proteins as claimed. Applicants respectfully request reconsideration and withdrawal of the rejection of claim 5 under 35 U.S.C. §112, first paragraph.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 1-3, 6 and 14 were rejected under 35 U.S.C. § 102(b) as being anticipated by Senoo et al., U.S. Patent No. 5,360,896 ("Senoo"). The Examiner alleged that Senoo teaches muteins of FGF in which a glycosylation site has been added, and that the glycosylated FGFs have improved properties such as increased stability, prolonged blood clearance time and improved activity. The Examiner stated that, since activity is retained, it is considered inherent that the muteins of Senoo have been "functionalized" as claimed, as the specification defines this term on page 7.

The Examiner rejected claim 2 alleging that the muteins of Senoo would have N-linked sugar chains. Claim 6 was also rejected because the Examiner alleged that the tertiary structure of the protein cannot be greatly changed if activity is retained in the muteins. With respect to claim 5, the Examiner stated that base claim 4 has limitations not taught or suggested by Senoo, who do not teach providing sugar chains bonded to a peptide which in turn is bonded to the FGF, and that for this reason part (a) of claim 5 is also not taught by Senoo. However, part (b) of claim 5 was rejected because the Examiner alleged "the recited SEQ ID NOS include a sequence derived from human acidic FGF," and because Senoo allegedly teaches "acidic FGF ... as a protein from which muteins with added glycosylation site(s) may be obtained." The Examiner noted that "the sequences recited in claim 5 include only a portion of the acidic FGF sequence and a portion of a protein with glycosylation sites (e.g. ryudocan)", but that "part (b) of claim 5 is sufficiently broad as to the number of deletions, substitutions and insertions that may be provided in the recited SEQ ID NOS that it is proper to consider these as encompassing a mutein of acidic FGF taught by Senoo." The Examiner stated that, "for example, the ryudocan sequence could be

deleted, and the left out portion of acidic FGF would be added, and the glycosylation sites could be inserted with the result that the sequence would be within the scope of claim 5 part (b)."

Applicants respectfully traverse these rejections. First, with respect to the rejection of claims 1-2, Applicants have amended claim 1 to incorporate the features of canceled claim 2, except that the element "an N-linked sugar chain" has been removed from the Markush grouping as it originally appeared in claim 2. Accordingly, claim 1 now recites

> "A heparin binding protein comprising at least one covalently bonded sugar chain, wherein the at least one sugar chain is selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain and combinations thereof."

In contrast to amended claim 1, Senoo discusses muteins of FGF in which a glycosylation site is introduced. However, only N-linked sugar chain modification is contemplated by Senoo. For example, Senoo states as follows:

> The mutein of the present invention has had introduced at least one glycosylation site. The amino acid sequence of the original peptide or protein may be mutagenized. Such mutagenesis includes, for example, addition of an amino acid(s), deletion of a constituent amino acid(s) and substitution of a constituent amino acid(s) for another amino acid(s).
>
> The above glycosylation sites include a site in which an amino acid sequence constituting the glycosylation site is represented by the following formula:
>
> *Asn-X-Y*
>
> wherein X may be any amino acid residue, and Y is Thr, Ser or Cys.
>
> Specifically, any glycosylation site may be used, as long as it produces an amino acid sequence represented by Asn-X-Thr, Asn-X-Ser or Asn-X-Cys (wherein X may be any amino acid) in the molecule. It has been known that some kind of regularity exists for the site of a protein to which a glycosyl chain is ligated in a glycoprotein. Namely, the glycosyl chain is ligated to the Asn residue of the protein. The amino acid sequence containing this Asn residue is a sequence called asparagine sequon, which is represented by a sequence consisting of the above three amino acids. These are described in FEBS Letters 108, 341 (1979), Biochem. J. 203, 761 (1982), Biochem. J. 209, 331 (1983) and FEBS Letters 96, 179 (1987).

U.S. Patent No. 5,360,896 (Senoo), col.4, line 62 - col. 5, line 22 (Emphasis added). It is clear

that Senoo describes glycosylation which is limited to Asparagine residues, i.e. N-linked glycosylation. Therefore, Senoo does not teach or suggest the heparin-binding protein of the amended claim 1, wherein N-linked glycosylation is not included within the group of potential covalently bonded sugar chains. Claims 3, 5, 6 and 14 all depend from amended claim 1, which Applicant believes is now allowable over the prior art. Accordingly, once base claim 1 is allowable over the prior art, its dependent claims 3, 5, 6 and 14 should also be allowable over the prior art.

In addition, Applicants traverse the rejection with respect to claim 5, which depends from claim 4. The Examiner has indicated that claim 4 contains allowable subject matter. However, the Examiner somehow then rejected part (b) of claim 5 over the prior art, while stating that part (a) is allowable over the prior art. Applicant submits that if base claim 4 is allowable over the prior art, then its dependent claims in their entireties are also allowable over the prior art. Thus, since claim 4 and part (a) of claim 5 are both allowable over the prior art, then part (b) of claim 5 should also be allowable over the same prior art. Accordingly, Applicants respectfully request that this rejection of claim 5 be withdrawn.

Therefore, Senoo does not teach or suggest the heparin-binding protein of the present claims. Applicants respectfully submit that the rejections of claims 1, 3, 6 and 14 under 35 U.S.C. § 102(b) have been overcome and request that the rejections be withdrawn.

OTHER AMENDMENTS AND NEW CLAIMS PRESENTED

Aside from the addition of the limitation of claim 2 (now canceled) to claim 1, claim 1 has been amended to modify the "sugar chain" with the addition of the term "at least one" to broaden the claim's scope and to allow for multiple sugar chains to be covalently bonded to the heparin-binding protein. Similarly, dependent claims 4, 5 and 6 have also been amended to refer to "at least one" covalently bonded sugar chain for proper antecedent basis. Claim 5, part (b) has been amended merely for clarification of language and to substitute "at least one amino acid" for the alternative "one or several amino acids."

New claims 16-21 have been added to more particularly claim the subject matter that Applicants regard as their invention. New claims 16, 17 and 19 now include the limitations of original claims 1, 2 and 4, and claim 18 has been added to make claim 4, which the Examiner stated contained allowable subject matter, into independent form. Similarly, new claims 20 and 21 include the limitations of claims 1 and 4. All of these new claims 16-21 patentably distinguish over Senoo, because Senoo contemplates only glycosylation of mutagenized FGF, and does not contemplate glycosylation of an extraneous peptide sequence which is not related to FGF in origin. It is apparent that the Examiner recognized this fact as well, because the Examiner stated:

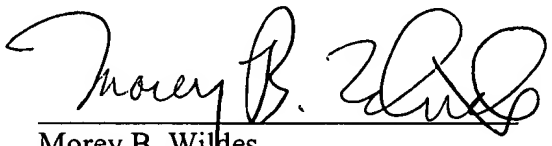
> Claim 4 has limitations not taught or suggested by Senoo et al, who do not teach providing sugar chains bonded to a peptide which in turn is bonded to the FGF. For this reason claim 5, part (a) is considered not taught by Senoo et al.

Office Action dated October 3, 2000, page 5. (Emphasis added). Accordingly, because new claims 16-21 contain this limitation that is not found in the prior art, these claims are allowable.

CONCLUSION

In view of the action taken and arguments made, Applicants believe that claims 1-6, 14 and 16-22 are patentable. An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC



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VERSION OF CLAIM AMENDMENTS
WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A heparin-binding protein comprising [functionalized by covalently bonding thereto a] at least one covalently bonded sugar chain, wherein the at least one sugar chain is selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain and combinations thereof.

3. (Amended) The heparin-binding protein of claim 1 [or 2], wherein the heparin-binding protein is a factor belonging to the FGF family [or its allied factor].

4. (Amended) The heparin-binding protein of claim 1, wherein the at least one sugar chain is covalently bonded [thereto] through a peptide to which the at least one sugar chain can be added.

5. (Amended) The heparin binding protein of claim 4, wherein the heparin-binding protein [to which] comprising the at least one covalently bonded sugar chain [is to be covalently bonded is the following (a) or (b)] comprises:

(a) a protein consisting of the amino acid sequence of SEQ ID NO: 1, [3, 5,] 17, 19, 21, 23, [25, 27] or 29; or

(b) a protein which consists of the amino acid sequence of SEQ ID NO: 1, [3, 5,] 17, 19, 21, 23, [25, 27] or 29 having a deletion, substitution, addition or modification of at least one [or several] amino acid [acids], wherein the heparin-binding protein [which] has FGF activity and [to which] the sugar chain can be added thereto.

6. (Amended) The heparin binding protein of claim 1, wherein the at least one sugar chain is bonded to the heparin-binding protein at a site forming a turn in the secondary structure, or at a site near one of the ends, or at a site at which addition of the sugar chain will not

change the tertiary structure of said protein greatly [by addition of the sugar chain].

14. (Amended) A pharmaceutical composition containing the heparin-binding protein of any one of claims [1-6] 1 and 3-6 as an active ingredient.